Ungar, Susan

To: STIC-ILL
Subject: Papers for Examination of SN 09/234,290

6/13/03

Hi

This is a RUSH , the case is due this biweek.

1. I need Cohen et al (Autoimmune Disease Models, A Guidebook, Academic Press, San Diego, 1994) I need the entire volume

2. Clinical and Experimental Immunology, 1999, 115(2)260-267

3. Annals of the NY Academy of Sicences, 2001, 928:200-211

4.Pancreas, 1999, 18(3)282-293

5. Pancrease, 2000, 20(2)197-205

6. Histochemical Journal, 2000, 32(4)195-206

7. Biochemical Society Transactions, 1997, 25(2)620-624

8. J. Clin. Investigation, 2001, 108(1)31-33

9.Diabetes Care, 1999, 22 Suppl 2 B7-B15

10. Immunological Reviews, 1999, 169:11-22

11.Immunological Reviews, 2000, 173:109-119

12. Diabetes/Metabolism Research and Reviews, 2001, 17(6)429-435 *********

Thanks
Susan Ungar
1642
703-305-2181
CM1-8B05

*Glutamate Decarboxylase: IM, immunology
Glutamate Decarboxylase: ME, metabolism
Islets of Langerhans: IM, immunology
Islets of Langerhans: PA, pathology
Isoenzymes: IM, immunology
Isoenzymes: ME, metabolism
Macrophages: IM, immunology
Macrophages: SE, secretion
Membrane Glycoproteins: SE, secretion
Membrane Proteins: IM, immunology
Membrane Proteins: ME, metabolism
Mice
Mice, Inbred NOD
Mice, SCID
Protein-Tyrosine-Phosphatase: IM, immunology
Protein-Tyrosine-Phosphatase: ME, metabolism
Rats
Rats, Inbred BB
Serine Endopeptidases: SE, secretion
T-Lymphocyte Subsets: IM, immunology
T-Lymphocyte Subsets: PA, pathology
T-Lymphocyte Subsets: SE, secretion

RN 126465-35-8 (perforin)
CN 0 (Autoantibodies); 0 (Autoantigens); 0 (Cytokines); 0 (ICA512 autoantibody); 0 (Isoenzymes); 0 (Membrane Glycoproteins); 0 (Membrane Proteins); EC 3.1.3.- (IA-2 protein); EC 3.1.3.48 (Protein-Tyrosine-Phosphatase); EC 3.4.21 (Serine Endopeptidases); EC 4.1.1.- (GAD65 enzyme); EC 4.1.1.- (GAD67 enzyme); EC 4.1.1.15 (Glutamate Decarboxylase)

L45 ANSWER 3 OF 21 MEDLINE
AN 2002045157 MEDLINE
DN 21628976 PubMed ID: 11757078
TI Clinical application of NKT cell assays to the prediction of type 1 **diabetes**.
AU Poulton L D; Baxter A G
CS Centenary Institute of Cancer Medicine and Cell Biology, Newtown, NSW, Australia.
SO DIABETES/METABOLISM RESEARCH AND REVIEWS, (2001 Nov-Dec) 17 (6) 429-35.
Ref: 81
Journal code: 100883450. ISSN: 1520-7552.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020124
Last Updated on STN: 20020403
Entered Medline: 20020329
AB Type 1 **diabetes** is a disease characterised by disturbed glucose homeostasis, which results from autoimmune destruction of the insulin-producing beta cells in the pancreas. The autoimmune attack, while not yet fully characterised, exhibits components of both mis-targeting and failed tolerance induction. The involvement of non-classical lymphocytes in the induction and maintenance of peripheral tolerance has recently been recognised and natural killer T (NKT) cells appear to play such a role. NKT cells are a subset of T cells that are distinct in being able to produce cytokines such as IL-4 and IFN-gamma extremely rapidly following activation. These lymphocytes also express some surface receptors, and the lytic activity, characteristic of NK cells. Deficiencies in NKT cells have been identified in animal models of type 1 **diabetes**, and a causal association has been demonstrated

Pancreas: PA, pathology
Spleen: CY, cytology
Spleen: TR, transplantation
T-Lymphocyte Subsets: IM, immunology
T-Lymphocyte Subsets: ME, metabolism
T-Lymphocyte Subsets: PA, pathology
*Trans-Activators: DF, deficiency
*Trans-Activators: GE, genetics
CN 0 (CIITA protein); 0 (Histocompatibility Antigens Class II); 0 (Trans-Activators)

L46 ANSWER 70 OF 169 MEDLINE
AN 1999132256 MEDLINE
DN 99132256 PubMed ID: 9933451
TI The pathogenicity of islet-infiltrating lymphocytes in the **non-obese diabetic** (**NOD**) mouse.
AU Ablamunits V; Elias D; Cohen I R
CS Department of Immunology, the Weizmann Institute of Science, Rehovot, Israel.
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1999 Feb) 115 (2) 260-7. Journal code: 0057202. ISSN: 0009-9104.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199903
ED Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990301
AB The aim of the present study was to investigate the pathogenic properties of islet-infiltrating lymphocytes related to the severity of the autoimmune destruction of islet beta-cells in the **NOD** mouse. We analysed the development of insulin-dependent **diabetes** mellitus (IDDM) produced by **adoptive transfer** of islet lymphocytes from **NOD** into **NOD**.scid mice. Here we show that the transfer was most effective when both CD4+ and CD8+ T cells were present in the infiltrate, but CD4+ T cells alone were sufficient to cause the disease. Islet lymphocytes from both females and males transferred **diabetes** effectively, but the severity of IDDM was higher when female islet lymphocytes were used. Unexpectedly, the sensitivity of male islets to beta-cell damage was greater than that of female islets. Treatment of **NOD** females with a peptide of heat shock protein (hsp)60, p277, known to protect **NOD** mice from IDDM, reduced the pathogenicity of the islet lymphocytes. In contrast, administration of cyclophosphamide to males, a treatment that accelerates the disease, rendered the islet lymphocytes more pathogenic. More severe disease in the recipient **NOD**.scid mice was associated with more interferon-gamma (IFN-gamma)-secreting islet T cells of the **NOD** donor. The disease induced by islet lymphocytes was strongly inhibited by co-transfer of spleen cells from **prediabetic** mice, emphasizing the regulatory role of peripheral lymphocytes. Thus, the cellular characteristics of the islet infiltrate and the pathogenicity of the cells are subject to complex regulation.
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
Adoptive Transfer
CD4-Positive T-Lymphocytes: IM, immunology
CD8-Positive T-Lymphocytes: IM, immunology
Cell Movement
Cyclophosphamide
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
Heat-Shock Proteins: PD, pharmacology
Insulin: IP, isolation & purification
Islets of Langerhans: CH, chemistry

TI Cellular and molecular pathogenic mechanisms of insulin-dependent **diabetes** mellitus.
AU Yoon J W; Jun H S
CS Department of Microbiology and Infectious Disease, Julia McFarlane Diabetes Research Centre, Faculty of Medicine, The University of Calgary, Alberta, Canada.. yoon@ucalgary.ca
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2001 Apr) 928 200-11. Ref: 52
Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020125
Last Updated on STN: 20020223
Entered Medline: 20020222
AB Insulin-dependent **diabetes** mellitus (IDDM), also known as type 1 **diabetes**, is an organ-specific autoimmune disease resulting from the destruction of insulin-producing pancreatic beta cells. The hypothesis that IDDM is an autoimmune disease has been considerably strengthened by the study of animal models such as the **BioBreeding** (**BB**) rat and the **nonobese diabetic** (**NOD**) mouse, both of which spontaneously develop a **diabetic** syndrome similar to human IDDM. Beta cell autoantigens, macrophages, dendritic cells, B lymphocytes, and T cells have been shown to be involved in the pathogenesis of autoimmune **diabetes**. Among the beta cell autoantigens identified, glutamic acid decarboxylase (GAD) has been extensively studied and is the best characterized. Beta cell-specific suppression of GAD expression in **NOD** mice results in the prevention of IDDM. Macrophages and/or dendritic cells are the first cell types to infiltrate the pancreatic islets. Macrophages play an essential role in the development and activation of beta cell-cytotoxic T cells. B lymphocytes play a role as antigen-presenting cells, and T cells have been shown to play a critical role as final effectors that kill beta cells. Cytokines secreted by immunocytes, including macrophages and T cells, may regulate the direction of the immune response toward Th1 or Th2 as well as cytotoxic effector cell or suppressor cell dominance. Beta cells are destroyed by apoptosis through Fas-Fas ligand and TNF-TNF receptor interactions and by granzymes and perforin released from cytotoxic effector T cells. Therefore, the activated macrophages and T cells, and cytokines secreted from these immunocytes, act synergistically to destroy beta cells, resulting in the development of autoimmune IDDM.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Adoptive Transfer
Antigen Presentation
Apoptosis
Autoantibodies: IM, immunology
*Autoantigens: IM, immunology
Autoantigens: ME, metabolism
Autoimmune Diseases: GE, genetics
*Autoimmune Diseases: IM, immunology
Autoimmune Diseases: ME, metabolism
Autoimmune Diseases: PA, pathology
B-Lymphocyte Subsets: IM, immunology
Cytokines: PH, physiology
Dendritic Cells: IM, immunology
Diabetes Mellitus, Insulin-Dependent: GE, genetics
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
Diabetes Mellitus, Insulin-Dependent: ME, metabolism
Diabetes Mellitus, Insulin-Dependent: PA, pathology

islet Ag-specific Vbeta4 T cell repertoire by breeding Ins-IL-10+/BALB/c mice with BDC2.5 mice. The progeny (Ins-IL-10+/BALB/c x BDC2.5+)F1 mice doubly tg for IL-10 and Vbeta4 (BDC2.5) T cell repertoire, developed **diabetes** at 10 to 18 weeks of age with a much more aggressive T cell infiltrate in the pancreatic islets than in single tg mice. Surprisingly, these **diabetic** mice were free from acute pancreatitis but had apoptotic beta cells in the islet infiltrate. Conversely, mice tg for Vbeta4 (BDC2.5) T cell repertoire but not IL-10 had no **diabetes** and no apoptotic beta cells in the islet infiltrate. Therefore, an increase in the frequency of islet-specific T cells apparently overcomes the protection from **diabetes** by a resistant genetic background. Interestingly, N2 backcross mice doubly tg for Vbeta4 (BDC2.5) T cell repertoire and IL-10, compared to N2 backcross mice tg for IL-10 only, eventually became **diabetic** but with a delayed onset and reduced incidence of disease. These findings demonstrate that, along with IL-10, an increase in frequency of islet antigen-specific T cells (a) overrides the protective effect of genetic resistance to autoimmune **diabetes** in F1 mice and (b) delays the onset of an otherwise accelerated **diabetes** in (Ins-IL-10+/**NOD**)N2 backcross mice.

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CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Adoptive Transfer
Age of Onset
Blood Glucose: AN, analysis
Crosses, Genetic
Cyclophosphamide: PD, pharmacology
***Diabetes Mellitus, Insulin-Dependent: GE, genetics**
Diabetes Mellitus, Insulin-Dependent: IM, immunology
*Gene Rearrangement, T-Lymphocyte
*Genetic Predisposition to Disease
*Interleukin-10: BI, biosynthesis
Interleukin-10: GE, genetics
Major Histocompatibility Complex
Mice
Mice, Inbred BALB C
Mice, Inbred NOD
Mice, Transgenic
Radiation Chimera
*Receptors, Antigen, T-Cell, alpha-beta: GE, genetics
Spleen: CY, cytology
Spleen: TR, transplantation
Variation (Genetics)

RN 130068-27-8 (Interleukin-10); 50-18-0 (Cyclophosphamide)
CN 0 (Blood Glucose); 0 (Receptors, Antigen, T-Cell, alpha-beta)

L46 ANSWER 67 OF 169 MEDLINE
AN 1999221328 MEDLINE
DN 99221328 PubMed ID: 10206487
TI The role of CD8+ cells, cell degeneration, and Fas ligand in insulitis after intraperitoneal transfer of **NOD** splenocytes.
AU Sainio-Pollanen S; Liukas A; Pollanen P; Simell O
CS Department of Anatomy, University of Turku, Finland.
SO PANCREAS, (1999 Apr) 18 (3) 282-93.
Journal code: 8608542. ISSN: 0885-3177.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; AIDS
EM 199906
ED Entered STN: 19990628
Last Updated on STN: 19990628

interaction in pancreatic beta cell apoptosis. However, recent works demonstrated that FasL is not an effector molecule in islet beta cell death. We addressed why **diabetes** cannot be transferred to **NOD**-lpr mice despite the nonessential role of Fas in beta cell apoptosis. Lymphocytes from **NOD**-lpr mice were constitutively expressing FasL. A decrease in the number of FasL+ lymphocytes by neonatal thymectomy facilitated the development of insulitis. Cotransfer of FasL+ lymphocytes from **NOD**-lpr mice completely abrogated **diabetes** after **adoptive transfer** of lymphocytes from **diabetic NOD** mice. The inhibition of **diabetes** by cotransferred lymphocytes was reversed by anti-FasL Ab, indicating that FasL on abnormal lymphocytes from **NOD**-lpr mice was responsible for the inhibition of **diabetes** transfer. Pretreatment of lymphocytes with soluble FasL (sFasL) also inhibited **diabetes** transfer. sFasL treatment decreased the number of CD4+CD45RBlow cells and increased the number of propidium iodide-stained cells among CD4+CD45RBlow cells, suggesting that sFasL induces apoptosis on CD4+CD45RBlow "memory" cells. These results resolve the paradox between previous findings and suggest a new role for FasL in the treatment of autoimmune disorders. Our data also suggest that sFasL is involved in the deletion of potentially hazardous peripheral "memory" cells, contrary to previous reports that Fas on unmanipulated peripheral lymphocytes is nonfunctional.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
Adoptive Transfer
*Antigens, CD95: ME, metabolism
*Apoptosis: IM, immunology
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
Diabetes Mellitus, Insulin-Dependent: PA, pathology
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Immunologic Memory: IM, immunology
Ligands
Lymphocytes: IM, immunology
Lymphocytes: ME, metabolism
Membrane Glycoproteins: BI, biosynthesis
*Membrane Glycoproteins: PH, physiology
Mice
Mice, Inbred C57BL
Mice, Inbred MRL lpr
Mice, Inbred NOD
Solubility
Spleen: CY, cytology
Spleen: IM, immunology

CN 0 (Antigens, CD95); 0 (FasL protein); 0 (Ligands); 0 (Membrane Glycoproteins)

L46 ANSWER 50 OF 169 MEDLINE
AN 2000170210 MEDLINE
DN 20170210 PubMed ID: 10707937
TI The role of lipid antigen presentation, cytokine balance, and major histocompatibility complex in a novel murine model of **adoptive transfer** of insulitis.
AU Ylinen L; Teros T; Liukas A; Arvilommi P; Sainio-Pollanen S; Verajankorva E; Pollanen P; Simell O
CS Department of Pediatrics, University of Turku, Finland.. laelyl@utu.fi
SO PANCREAS, (2000 Mar) 20 (2) 197-205.
Journal code: 8608542. ISSN: 0885-3177.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000327

L46 ANSWER 41 OF 169 MEDLINE
AN 2001021307 MEDLINE
DN 20329285 PubMed ID: 10872884
TI Temporal relationship between immune cell influx and the expression of inducible nitric oxide synthase, interleukin-4 and interferon-gamma in pancreatic islets of **NOD** mice following **adoptive transfer** of **diabetic** spleen cells.
AU Reddy S; Karanam M; Krissansen G; Nitschke K; Neve J; Poole C A; Ross J M
CS Department of Paediatrics, University of Auckland School of Medicine, New Zealand.
SO HISTOCHEMICAL JOURNAL, (2000 Apr) 32 (4) 195-206.
Journal code: 0163161. ISSN: 0018-2214.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001107
AB Beta cell destruction in **NOD** mice can be accelerated by **adoptive transfer** of **diabetic** spleen cells into irradiated adult **NOD** mice. Here mice receiving **diabetic** spleen cells were examined at days 0, 7, 14, 21 and at onset of **diabetes** for the resulting insulitis and the number of intra-islet CD4 and CD8 cells and macrophages. The progression of insulitis and the number of intra-islet CD4 and CD8 cells and macrophages were correlated with the expression and co-localization of inducible nitric oxide synthase, interferon-gamma and interleukin-4 by dual-label light and confocal immunofluorescence microscopy. **Diabetes** developed in 7/8 mice by 27 days following cell transfer. The insulitis score increased slightly by day 7 but rose sharply at day 14 ($p = 0.001$) and was maintained until **diabetes**. The mean number of intra-islet CD4 and CD8 cells and macrophages showed a similar trend to the insulitis scores and were present in almost equal numbers within the islets. Immunolabelling for inducible nitric oxide synthase was observed at day 7 in only some cells of a few islets but increased sharply from day 14. It was restricted to islets with insulitis and was co-localized in selective macrophages. Weak intra-islet interleukin-4 labelling was observed at days 7 and 14 but became more pronounced at day 21 and at onset of **diabetes**, being present in selective CD4 cells. Intra-islet labelling for interferon-gamma was first observed at day 21, but became more intense at onset of **diabetes** and was co-localized in a proportion of macrophages. Both cytokines were expressed in islets with advanced insulitis. Interferon-gamma staining was also observed within endothelial cells located in the exocrine pancreas. We conclude that transfer of **diabetic** spleen cells results in a rapid influx of CD4 and CD8 cells and macrophages within the pancreas of recipient mice. During the period of heightened insulitis, selective immune cells begin to express inducible nitric oxide synthase and the opposing cytokines, interferon-gamma and interleukin-4. Expression of these molecules becomes more pronounced immediately prior to and during the onset of **diabetes**.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Adoptive Transfer
CD4-Positive T-Lymphocytes: CY, cytology
*CD4-Positive T-Lymphocytes: IM, immunology
CD8-Positive T-Lymphocytes: CY, cytology
*CD8-Positive T-Lymphocytes: IM, immunology
Cell Transplantation
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
Glucagon: BI, biosynthesis

L44 ANSWER 5 OF 12 MEDLINE
AN 97334502 MEDLINE
DN 97334502 PubMed ID: 9191169
TI Immune deviation towards Th2 inhibits Th-1-mediated autoimmune **diabetes.**
AU Adorini L; Trembleau S
CS Roche Milano Ricerche, Italy. .
SO BIOCHEMICAL SOCIETY TRANSACTIONS, (1997 May) 25 (2) 625-9. Ref: 58
Journal code: 7506897. ISSN: 0300-5127.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 199708
ED Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970804
CT Check Tags: Animal; Female; Human
Adoptive Transfer
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: PD, pharmacology
Lymphocyte Transfusion
Mice
Mice, Inbred NOD
*Th1 Cells: IM, immunology
*Th2 Cells: IM, immunology
RN 187348-17-0 (Interleukin-12)

L44 ANSWER 6 OF 12 MEDLINE
AN 97334501 MEDLINE
DN 97334501 PubMed ID: 9191168
TI Role of CD4+CD8- thymocytes in the prevention of autoimmune **diabetes.**
AU Seddon B; Mason D
CS Medical Research Council Cellular Immunology Unit, Sir William Dunn School of Pathology, University of Oxford, U.K.
SO BIOCHEMICAL SOCIETY TRANSACTIONS, (1997 May) 25 (2) 620-4. Ref: 16
Journal code: 7506897. ISSN: 0300-5127.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970804
CT Check Tags: Animal; Female; Human; Male
***Adoptive Transfer**
*CD4-Positive T-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: RE, radiation effects
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Lymphocyte Depletion
Rats
Rats, Inbred Strains
Self Tolerance
*T-Lymphocyte Subsets: IM, immunology

Lymphocytes: IM, immunology
Lymphokines: BI, biosynthesis
Mice
Rats
Rats, Brattleboro
Stress: CO, complications
Virus Diseases: CO, complications
CN 0 (Autoantibodies); 0 (HLA Antigens); 0 (Immunosuppressive Agents); 0 (Lymphokines); 0 (islet cell antibody)

=> d all tot l44

L44 ANSWER 1 OF 12 MEDLINE
AN 2003106844 MEDLINE
DN 22506694 PubMed ID: 12619718
TI Utilization of **NOD** mice in the study of type 1 **diabetes**
.
AU Karounos Dennis G; Goes Susan E
CS Medical Service, Department of Veterans Affairs Medical Center, University of Kentucky College of Medicine, Lexington, USA.
SO Methods Mol Med, (2003) 83 81-90.
Journal code: 101123138.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030307
Last Updated on STN: 20030418
Entered Medline: 20030417
CT Check Tags: Animal; Human
Adoptive Transfer
Blood Glucose: ME, metabolism
Blood Specimen Collection: MT, methods
***Diabetes Mellitus, Insulin-Dependent**
Diabetes Mellitus, Insulin-Dependent: BL, blood
Diabetes Mellitus, Insulin-Dependent: DI, diagnosis
Diabetes Mellitus, Insulin-Dependent: IM, immunology
Disease Models, Animal
Enzyme-Linked Immunosorbent Assay: MT, methods
Indicators and Reagents
Insulin: AN, analysis
Insulin: TU, therapeutic use
Islets of Langerhans: PA, pathology
Mice
Mice, Inbred NOD
T-Lymphocytes: IM, immunology
RN 11061-68-0 (Insulin)
CN 0 (Blood Glucose); 0 (Indicators and Reagents)

L44 ANSWER 2 OF 12 MEDLINE
AN 2001379141 MEDLINE
DN 21329128 PubMed ID: 11435453
TI Immunomodulatory therapy of human type 1 **diabetes**: lessons from the mouse.
CM Comment on: J Clin Invest. 2001 Jul;108(1):63-72
AU Palmer J P
CS Department of Medicine, University of Washington, Seattle, USA.. jpp@u.washington.edu
SO JOURNAL OF CLINICAL INVESTIGATION, (2001 Jul) 108 (1) 31-3.
Journal code: 7802877. ISSN: 0021-9738.
CY United States

ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990527

AB **Diabetes** type 1A is an autoimmune condition characterized by lymphocytic infiltration of islets and selective destruction of insulin-secreting beta-cells. Numerous investigators have prevented **diabetes** in animal models with a variety of antigens and routes of administration. It is also now possible to identify high-risk individuals even before the appearance of autoantibodies. These advances have created the opportunity to design and begin human prevention trials. This **review** focuses on a variety of immunomodulatory approaches (including administration of adjuvants, autoantigens, T-cells, T-cell receptors, and DNA) that we have collectively termed immunologic "vaccination." In addition, we discuss the potential benefits and dangers of these approaches and issues relating to the design of human trials.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adjuvants, Immunologic: TU, therapeutic use
Adoptive Transfer
Autoantigens: IM, immunology
Diabetes Mellitus, Insulin-Dependent: IM, immunology
***Diabetes Mellitus, Insulin-Dependent: PC, prevention & control**
Receptors, Antigen, T-Cell: IM, immunology
Research Design
T-Lymphocytes: IM, immunology
*Vaccination
Vaccines, DNA

CN 0 (Adjuvants, Immunologic); 0 (Autoantigens); 0 (Receptors, Antigen, T-Cell); 0 (Vaccines, DNA)

L45 ANSWER 9 OF 21 MEDLINE
AN 1999009653 MEDLINE
DN 99009653 PubMed ID: 9793258
TI Stem cell transplantation for severe autoimmune diseases: progress and problems.
AU Marmont A M
CS II Division of Hematology, S. Martino's Hospital, Genoa, Italy.
SO HAEMATOLOGICA, (1998 Aug) 83 (8) 733-43. Ref: 148
Journal code: 0417435. ISSN: 0390-6078.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981214

AB Since Morton and Siegel's epochal experiments 30 years ago animal models have been successfully utilized both for transfer and resolution of autoimmune diseases (AID). More recently human lymphocyte xenografts have reproduced clinical AID in SCID mice. Allogeneic stem cell transplantation demonstrated therapeutic potential in fully developed autoimmune disease. Mixed allogeneic chimerism induced by a sublethal approach has also been shown to prevent and even reverse autoimmune insulitis in **nonobese diabetic** (**NOD**) mice.
More unexpectedly it was found that experimental adjuvant arthritis (AA) and experimental allergic encephalomyelitis (EAE) could be cured by means of total body irradiation (TBI) followed by autologous hemolymphopoietic stem cell (HSC) transplantation. It was postulated that the newly developing T cells might be tolerant to self antigens. The transfer of AID from affected donors to recipients of allogeneic HSC transplants has been reported for many organ-specific AID, including **diabetes**

CS Department of Neurology, Kyoto University.
SO RINSHO SHINKEIGAKU. CLINICAL NEUROLOGY, (1998 Dec) 38 (12) 969-73. Ref: 14
Journal code: 0417466. ISSN: 0009-918X.
CY Japan
DT (LECTURES)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 199909
ED Entered STN: 19991012
Last Updated on STN: 19991012
Entered Medline: 19990924
AB In addition to the traditional preoccupation for accurate localization of lesions, a new trend in our discipline emphasizes therapeutic approaches to various neurological disorders. This **review** summarizes the result of multi-center trials that we personally participated during the past decade to present an overview of the current thought in the area of our interest. The disorders in question include dystonia, chronic inflammatory demeyelinating polyneuropathy, myoclonic epilepsy, **diabetic** polyneuropathy, amyotrophic lateral sclerosis, and experimental allergic neuritis. These results and other equally encouraging data suggest that we are not necessarily fighting a loosing battle in dealing with these incapacitating diseases, even though our effort often falls short of achieving a complete cure. In formulating a list of differential diagnosis, we must always entertain the possibility of remedy as the eventual goal of our clinical practice.
CT Check Tags: Human
Afferent Pathways
*Botulinum Toxins: TU, therapeutic use
Cyclooxygenase Inhibitors: TU, therapeutic use
English Abstract
Immunization, Passive
Multicenter Studies
*Muscular Diseases: TH, therapy
*Nerve Block
Nerve Block: MT, methods
Neurology
Peripheral Nervous System Diseases: TH, therapy
CN 0 (Botulinum Toxins); 0 (Cyclooxygenase Inhibitors)

L45 ANSWER 8 OF 21 MEDLINE
AN **1999197966** MEDLINE
DN **99197966** PubMed ID: **10097893**
TI Immunologic "vaccination" for the prevention of autoimmune **diabetes** (type 1A).
AU Simone E A; Wegmann D R; Eisenbarth G S
CS Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver 80262.
NC R01AI39213 (NIAID)
R37 DK32083 (NIDDK)
RO1DK47298 (NIDDK)
+
SO DIABETES CARE, (1999 Mar) 22 Suppl 2 B7-15. Ref: 102
Journal code: 7805975. ISSN: 0149-5992.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199905

Connecticut 06520, USA.
NC P01 DK53015 (NIDDK)
R01 DK51665 (NIDDK)
SO IMMUNOLOGICAL REVIEWS, (1999 Jun) 169 11-22. Ref: 107
Journal code: 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991018
AB In the past decade, a wealth of information has accumulated through studies in **non-obese diabetic** (**NOD**) mice regarding the molecular and cellular events that participate in the progression to **diabetes** in insulin-dependent **diabetes** mellitus (IDDM). One molecule that has received considerable attention is the inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha). TNF-alpha has been demonstrated to have a positive or negative effect on the progression to **diabetes** in **NOD** mice, although the mechanism by which TNF-alpha exerts these differential outcomes is unknown. Here we describe a new **NOD** model for analyzing the role of TNF-alpha in IDDM, TNF-alpha-**NOD** mice. TNF-alpha-**NOD** mice express TNF-alpha solely in their islets from neonatal life onwards, and develop accelerated progression to **diabetes**. This rapid progression to **diabetes** is related to earlier and more aggressive infiltration of the islets with immune cells and an enhancement in the presentation of islet antigen in situ in the islets by islet-infiltrating antigen-presenting cells to T cells. Although **adoptive transfer** studies demonstrated that TNF-alpha can enhance presentation of islet antigen to both effector CD4+ and CD8+ T cells, further investigations in TNF-alpha-**NOD** mice deficient in either CD4+ or CD8+ T cells demonstrated that **diabetes** progression is dependent on CD8+ T cells, with CD4+ T cells playing a lesser role. The data accumulating from TNF-alpha-**NOD** mice, described in this **review**, indicates novel pathways by which inflammatory stimuli can precipitate autoimmunity, and suggests newer approaches in the design of therapeutic treatments that prevent beta-cell destruction in IDDM.
CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals, Newborn
Antigen Presentation
Autoimmunity
***Diabetes Mellitus, Insulin-Dependent: ET, etiology**
Diabetes Mellitus, Insulin-Dependent: IM, immunology
Diabetes Mellitus, Insulin-Dependent: PC, prevention & control
Disease Models, Animal
Islets of Langerhans: IM, immunology
Lymphocytes: IM, immunology
Mice
Mice, Inbred NOD
Tumor Necrosis Factor: AI, antagonists & inhibitors
*Tumor Necrosis Factor: IM, immunology
CN 0 (Tumor Necrosis Factor)

L45 ANSWER 7 OF 21 MEDLINE
AN 1999278949 MEDLINE
DN 99278949 PubMed ID: 10349332
TI Therapy oriented neurology from repair to remedy.
AU Kimura J

L45 ANSWER 5 OF 21 MEDLINE
AN 2000184586 MEDLINE
DN 20184586 PubMed ID: 10719672
TI Gamma delta T cells as mediators of mucosal tolerance: the autoimmune **diabetes** model.
AU Hanninen A; Harrison L C
CS Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Australia.
SO IMMUNOLOGICAL REVIEWS, (2000 Feb) 173 109-19. Ref: 80
Journal code: 7702118. ISSN: 0105-2896.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB Mucosal delivery of soluble antigen induces systemic tolerance and has been applied to the prevention of autoimmune diseases. We have studied mucosal tolerance in autoimmune **diabetes** using the **non -obese diabetic** mouse model. Treatment of **prediabetic** mice with the pancreatic islet autoantigen insulin, by aerosol or intranasal delivery, reduces the incidence of **diabetes** and is associated with induction of CD8 (alpha alpha) gamma delta T cells, small numbers of which prevent **adoptive transfer** of **diabetes**. We examine the evidence for gamma delta T cells in mucosal tolerance and discuss possible mechanisms underlying the induction and action of insulin-induced CD8 gamma delta regulatory T cells. CD8 gamma delta cells constitute the most abundant subpopulation of intraepithelial lymphocytes (IELs), the major lymphoid cell compartment and first line of cellular immune defence in the mucosa. Induction of regulatory CD8 gamma delta T cells requires conformationally intact but not biologically active insulin. In contrast, intranasal (pro)insulin peptide, or oral insulin which is degraded in the gut, induces CD4 regulatory cells. Regulatory gamma delta T cells secrete interleukin-10 in pancreatic lymph nodes, which could account for the **antidiabetic** and bystander suppressor effect of naso-respiratory insulin. The physiological role of gamma delta IELs in maintaining peripheral self-tolerance deserves further study.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Autoantigens: IM, immunology
Diabetes Mellitus, Insulin-Dependent: IM, immunology
***Diabetes Mellitus, Insulin-Dependent: TH, therapy**
*Immune Tolerance
Insulin: IM, immunology
Islets of Langerhans: IM, immunology
Mice
*Nasal Mucosa: IM, immunology
*Receptors, Antigen, T-Cell, gamma-delta
*T-Lymphocyte Subsets: IM, immunology
RN 11061-68-0 (Insulin)
CN 0 (Autoantigens); 0 (Receptors, Antigen, T-Cell, gamma-delta)

L45 ANSWER 6 OF 21 MEDLINE
AN 1999378998 MEDLINE
DN 99378998 PubMed ID: 10450504
TI Tumor necrosis factor-alpha and the progression of **diabetes** in **non-obese diabetic** mice.
AU Green E A; Flavell R A
CS Section of Immunobiology, Yale University School of Medicine, New Haven,

by **adoptive transfer** experiments in **diabetes**
-prone **NOD** mice. Preliminary work suggests that a similar
relationship may exist between deficiencies in NKT cells and type 1
diabetes in humans, although the techniques reported to date would
be difficult to translate to clinical use. Here, we describe methods
appropriate to the clinical assessment of NKT cells and discuss the steps
required in the assessment and validation of NKT cell assays as a
predictor of type 1 **diabetes**.
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CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Diabetes Mellitus, Insulin-Dependent: DI, diagnosis
***Diabetes Mellitus, Insulin-Dependent: IM, immunology**
Flow Cytometry
Interleukin-4: BL, blood
*Killer Cells, Natural: IM, immunology
Mice
Mice, Inbred NOD
Predictive Value of Tests
RN 207137-56-2 (Interleukin-4)

L45 ANSWER 4 OF 21 MEDLINE
AN 2000473047 MEDLINE
DN 20308952 PubMed ID: 10852112
TI Regulation of development and function of memory CD4 subsets.
AU Bradley L M; Harbertson J; Freschi G C; Kondrack R; Linton P J
CS Department of Immunology, The Scripps Research Institute, La Jolla, CA
92037, USA.. lbradley@scripps.edu
NC AI32978 (NIAID)
AI45812 (NIAID)
AI46530 (NIAID)
SO IMMUNOLOGIC RESEARCH, (2000) 21 (2-3) 149-58. Ref: 38
Journal code: 8611087. ISSN: 0257-277X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001004
AB Immunologic memory refers to the dramatic response to previously
encountered antigen (Ag) that is largely controlled by CD4 T cells.
Understanding how CD4 memory is regulated is essential for exploiting the
immune system to protect against disease and to dampen immunopathology in
allergic responses and autoimmunity. Using defined **adoptive-**
transfer models, we are studying parameters that affect
differentiation of memory CD4 cells in vivo and have found that a complex
interplay of T cell receptor signaling, costimulation, and cytokines can
determine the extent of memory development and the balance of Th1 and Th2
memory subsets. On challenge, memory CD4 cells localize in sites of Ag
exposure and develop into effectors that regulate memory responses. We
are investigating the roles of adhesion molecules, cytokines, and
chemokines in the selective recruitment of CD4 memory subsets to address
mechanisms by which memory T cells provide long-lasting immunity and, in
our recent studies, to determine how memory CD4 cells contribute to the
development of autoimmune **diabetes**.
CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
Cell Differentiation: IM, immunology
*Immunologic Memory
*T-Lymphocyte Subsets: IM, immunology